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Sex Differences in Comorbid Mental and Substance Use Disorders Among Primary Care Patients With Opioid Use Disorder

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Abstract

Objective: The authors sought to characterize the 3-year prevalence of mental disorders and nonnicotine substance use disorders among male and female primary care patients with documented opioid use disorder across large U.S. health systems.

Methods: This retrospective study used 2014–2016 data from patients ages ≥16 years in six health systems. Diagnoses were obtained from electronic health records or claims data; opioid use disorder treatment with buprenorphine or injectable extended-release naltrexone was determined through prescription and procedure data. Adjusted prevalence of comorbid conditions among patients with opioid use disorder (with or without treatment), stratified by sex, was estimated by fitting logistic regression models for each condition and applying marginal standardization.

Results: Females (53.2%, N=7,431) and males (46.8%, N=6,548) had a similar prevalence of opioid use disorder. Comorbid mental disorders among those with opioid use disorder were more prevalent among females (86.4% vs. 74.3%, respectively), whereas comorbid other substance use disorders (excluding nicotine) were more common among males (51.9% vs. 60.9%, respectively). These differences held for those receiving medication treatment for opioid use disorder, with mental disorders being more common among treated females (83% vs. 71%) and other substance use disorders more common among treated males (68% vs. 63%). Among patients with a single mental health condition comorbid with opioid use disorder, females were less likely than males to receive medication treatment for opioid use disorder (15% vs. 20%, respectively).

Conclusions: The high rate of comorbid conditions among patients with opioid use disorder indicates a strong need to supply primary care providers with adequate resources for integrated opioid use disorder treatment.

The United States continues to face an opioid crisis; from 2000 to 2014, the prevalence of opioid use disorders increased 125%, and opioid-related overdose deaths increased 200% (1, 2), even when levels of prescribing did not increase (3). Treatment for opioid use disorder in general medical settings may be more convenient and less stigmatizing for patients than in settings for specialized treatment for substance use and allows for interventions in the context of other health needs (4). At the same time, the burden on primary care continues to expand, straining resources (5). As primary care–based opioid use disorder treatment proliferates, understanding the landscape of disorder complexity among patients is important, as is identifying effective means of triage and resource allocation, including what is needed to successfully and comprehensively treat patients with opioid use disorder (6).

Mental disorders and other substance use disorders are common among patients with opioid use disorder (7-10) and may require protocols and clinical pathways that differ from standard treatment. Diagnoses of comorbid mental and substance use disorders are also associated with higher risk for relapse, nonadherence to medication treatment for opioid use

disorder (11, 12), and lower likelihood of completing treatment (13). Current estimates of these diagnoses among individuals with opioid use disorder range widely, however—from 25% to 90% for mental disorders (7, 8, 10, 14-17) and from 16% to 75% (7-9, 14, 15) for nonnicotine substance use disorders. Nearly all of these estimates come from studies of patients seeking opioid use disorder treatment and may not provide an accurate picture of primary care populations. Given the potential impact of these diagnoses on opioid use disorder treatment protocols, resource allocation, and patient outcomes, it is important to estimate their prevalence in the general population.

It is essential, however, to consider sex when examining the prevalence of mental health and substance use comorbidity among patients with opioid use disorder (18). Findings from national data of individuals with opioid use disorder indicate that females are twice as likely as males to have a mood or an anxiety disorder (19). Results of a pretreatment assessment of individuals with opioid use disorder indicated that females were more likely to test positive for amphetamines, methamphetamine, and phencyclidine, whereas males more commonly tested positive for alcohol, methadone, and cannabis use (20). In studies of opioid use disorder (21, 22) or general substance use disorders (20, 23), females reported current and past psychiatric problems more often than did males. Finally, females have reported greater functional impairment due to a substance use disorder or psychiatric symptoms (20, 23, 24).

A better understanding of sex-stratified rates of comorbid mental and substance use disorder diagnoses among patients with opioid use disorder (treated or untreated) is essential to further treatment efforts (18, 25). Our aim was to describe the 3-year prevalence of mental and nonnicotine substance use disorder diagnoses among male and female primary care patients with documented opioid use disorder—with and without medication treatment for opioid use disorder—across six diverse U.S. health systems.

METHODS

Settings

Six health systems contributed data for this retrospective cross-sectional study, including data from four Kaiser Permanente (KP) regional health systems (Washington State, Northwest [Oregon], Northern California, and Colorado), HealthPartners (Minnesota and Wisconsin), and MultiCare Health System (Washington State). The KP health systems and HealthPartners both insure and provide comprehensive care to their enrollees and receive claims from care delivered in external facilities. Three of the KP health systems (Northwest, Northern California, and Colorado) are integrated care systems, HealthPartners and KP Washington are mixed-model systems (integrated delivery system and contracted network providers and clinics), and MultiCare is a fee-for-service community health care system serving primarily urban and some rural populations. All six health systems use the Epic electronic health record (EHR) system. All except MultiCare are part of the Health Care Systems Research Network and thus have organized their EHR and claims data in a common data model (26); MultiCare data were translated to this format for analyses. The study was approved and monitored by the KP Washington Institutional Review Board.

Sample

The sample was identified from existing EHR and claims data in phase 1 of the Primary Care Opioid Use Disorders (PROUD) study, a National Institute on Drug Abuse–Clinical Trials Network–sponsored pragmatic, cluster-randomized controlled trial (protocol CTN-0074) of the efficacy of collaborative care for increasing access to and maintenance of medication for opioid use disorder in primary care (27). Phase 1 was a prerandomization pilot study to assess the feasibility of the health systems and their data for the trial (28, 29) and reflected sites different from those in the actual trial (27). This study sample included patients ages ≥16 years who made at least two primary care visits to the same participating health system between October 1, 2013, and September 30, 2016 (fiscal year [FY] 2014–2016). Two or more visits were required for inclusion to reduce the likelihood of including patients who were not regularly receiving care in the clinics. Four health systems included patients seen in all of their primary care clinics, one health system included patients seen in five large primary care clinics (≥20,000 patients per clinic), and another included patients seen in primary care clinics that were not close to or colocated with substance use disorder treatment services (five to 25 primary care clinics were included per health system).

Data Source and Measures

Data elements from EHR and claims data over the 3-year study period included patient demographic characteristics, diagnoses, and procedures, as well as pharmacy dispensings (five sites) or medication orders (one site), which are referred to as prescriptions hereafter. Demographic characteristics at the time of study entry (e.g., initial visit to a study clinic during the study period) included age, binary sex as recorded in the EHR (representing legal sex or sex assigned at birth), race-ethnicity, and health insurance type (which was missing for one site).

Visit-based diagnoses were based on *ICD-9-CM* (until September 30, 2015) or *ICD-10-CM* diagnostic codes (starting October 1, 2015). Mental disorders of interest included anxiety, depression, serious psychiatric illnesses (bipolar disorder and schizophrenia and other psychosis), attention-deficit hyperactivity disorder (ADHD), and eating disorders. Substance use disorders included use of alcohol, cannabis, stimulants, and other drugs. Nicotine use disorder was assessed separately. Patients were classified as having a documented opioid use disorder if they had an *ICD* code for opioid use disorder—including remission. Remission codes were included because diagnostic codes are applied inconsistently and accuracy of active and remission status in primary samples is unknown and because we were interested in characterizing comorbid conditions irrespective of active or remission status. A Charlson Comorbidity Index (CCI) score (30) was created by using diagnostic codes during the first FY of study entry. Diagnoses were derived from encounters occurring anywhere in the health system. The CCI score is a sum of 17 comorbid conditions that are weighted according to the relative risk for 1-year mortality (30, 31). A higher CCI score indicates increased disease burden and risk of death.

Opioid use disorder treatment was defined as any documented prescription of buprenorphine formulations (transmucosal, implant, or extended-release [XR] injection), with or without naloxone, indicated for treatment of opioid use disorder, at any time during the 3-year study

period throughout the health system. As a secondary treatment outcome, XR naltrexone use for opioid use disorder was determined from at least one procedure code or an XR naltrexone prescription plus an opioid use disorder diagnosis. Oral naltrexone was not included as opioid use disorder treatment because most oral naltrexone use is for alcohol use disorder (32, 33). Opioid use disorder treatment was restricted to these formulations because none of the health systems had internal federally approved methadone treatment programs.

Data Analytic Strategy

We used descriptive statistics to characterize the sample overall and by sex. The prevalence of mental and substance use disorder diagnoses was estimated among females and males with opioid use disorder by fitting separate logistic regression models for aggregates (e.g., any mental or substance use disorder diagnosis), as well as each mental and substance use disorder diagnosis, and then applying marginal standardization (34). Regression models included age in FY 2014 (modeled as a categorical variable), race-ethnicity, and health system. From the fitted models, we obtained marginal predictions (and 95% confidence intervals [CIs]) for females and males to describe the adjusted prevalence of diagnoses (35). The same approach was used to estimate the adjusted prevalence of mental and substance use disorder diagnoses (both as comorbid and individual disorders) for the subset of females and males with documented opioid use disorder who also received opioid use disorder medication treatment.

Finally, to assess whether comorbid diagnoses were associated with receipt of opioid use disorder treatment, we described the adjusted prevalence of opioid use disorder medication treatment across four mutually exclusive comorbidity groups on the basis of the presence of one or more mental or substance use disorder diagnoses. The four groups were the following: no mental or substance use disorder diagnosis, substance use disorder diagnoses only, mental disorder diagnoses only, and both mental and substance use disorder diagnoses. Prevalence of treatment (any opioid use disorder treatment, buprenorphine, or injectable XR naltrexone) was estimated in logistic regression models similar to those described above and that included an interaction term for sex and comorbidity group.

RESULTS

Overall, 1% (N=13,979) of the individuals in the total PROUD phase 1 sample (N=1,403,266) were classified as having an opioid use disorder, with similar prevalence among females (N=7,431, 53.2%) and males (N=6,548, 46.8%) (Table 1). Nearly 93% of opioid use disorder diagnoses captured in the study time frame were classified as active. The mean±SD age was 45.4617.0 years (range 16–98) and 42.4616.2 years (range 16–99) among females and males, respectively. Most patients with an opioid use disorder were White (78.6%), followed by Black (6.6%) and multiracial (3.3%), and 6.2% indicated Hispanic ethnicity. More than half of the patients were commercially insured, and nearly one-quarter (22.5%) received Medicare. Approximately 6% had a CCI score ≥2, and close to two-thirds (60.4%) had a nicotine use disorder.

Prevalence of Mental and Substance Use Disorder Diagnoses Among Females and Males With Opioid Use Disorder

Compared with males with opioid use disorder, females with opioid use disorder had higher rates of mental disorders, both overall (86.4% females and 74.3% males) and among four of the five distinct categories we examined (Table 2). Prevalence of ADHD (10.4% females and 11.5% males) was similar for the two groups. Compared with females, males had higher prevalence of other nonnicotine substance use disorders overall (51.9% females vs. 60.9% males) and for each disorder that involved alcohol, cannabis, stimulants, and other substances (Table 2). More females than males had a substance use disorder or psychiatric diagnosis (90.8% females and 85.9% males), but females and males had similar prevalence of having both a substance use disorder and mental disorder (47.5% females and 49.2% males).

Prevalence of Mental and Substance Use Disorders Among Females and Males Receiving Medication Treatment for Opioid Use Disorder

The prevalence of any mental disorders was 71% among males treated with medications for opioid use disorder and 83% among treated females (Table 3); prevalence of other nonnicotine substance use disorders was 68% and 63% among treated males and females, respectively. Females who received treatment were slightly more likely than males who received treatment to have a diagnosis of any comorbid mental or substance use disorder (90% vs. 86%). Only a small proportion of treated females (10%) and males (14%) had no mental or other substance use disorder diagnosis.

Prevalence of Opioid Use Disorder Treatment in Four Diagnosis Subgroups

No meaningful differences in medication treatment for opioid use disorder were detected across the various mental and substance use disorder subgroups (see Table S1 in an online supplement to this article). However, females with opioid use disorder but no other substance use disorder and who had additional mental health conditions (15%, 95% CI = 14%–16%) were less likely than males to receive opioid use disorder treatment (20%, 95% CI = 18%–22%).

DISCUSSION

In this large multisite observational study, diagnoses of mental and nonnicotine substance use disorders were common among both female and male primary care patients with a documented opioid use disorder. Females with opioid use disorder had a higher prevalence ofmental health conditions than males, and males with opioid use disorder had a higher prevalence of other substance use disorders than females. This sex-stratified pattern was also present among patients receiving medication treatment for opioid use disorder. Very few individuals receiving such medications were without a diagnosis of a comorbid mental or substance use disorder. Females in our sample with comorbid mental disorder only were less likely to receive medication treatment for opioid use disorder than were males with comorbid mental disorder only.

According to data from EHRs (16, 17), intake interviews (10), and chart reviews (7), rates of comorbid mental and opioid use disorders range from 66% to 79%, similar to the range in our sample (71%–83%). Rates of comorbid nonnicotine substance use disorders with opioid use disorder range from 16% to 75% (7-9, 14, 15), with higher rates among patients receiving office-based medication treatment and lower rates among individuals in mental health (15) or chronic pain treatment (9). The prevalence of nonnicotine substance use disorder comorbid with opioid use disorder was lower when a structured clinical interview, rather than health record data, was used (9, 14). We note that our estimates are based on a 3-year period, and opioid use disorder treatment was not restricted to primary care, whereas samples described in the literature consist almost exclusively of individuals seeking opioid use disorder treatment (vs. the general primary care population). Regardless, our estimates suggest that significant resources are needed for treating individuals with opioid use disorder in primary care. Collaborative care models may be useful, given the spread of responsibility across multiple providers and previous successes in primary care (36). Recent expansion of telemedicine services due to the COVID-19 pandemic (37) may improve primary care capacity to treat this population.

Consistent with studies reporting differences in mental health conditions and substance use disorder among sexes (38), females with opioid use disorder were more likely than males to have comorbid psychiatric diagnoses, whereas males with opioid use disorder were more likely to have comorbid substance use disorders (both for individuals with or without treatment for opioid use disorder). It is possible that the clinical setting in which individuals presented may have played a role in these sex differences. Females are more likely to present in primary care (39, 40), where providers may be more comfortable addressing mental disorders (41) rather than substance use disorders (42, 43). It was beyond the scope of this study to determine where diagnoses were originally documented, precluding conjecture about these sex-specific patterns aside from their similarity to general population trends.

Males and females appeared similarly likely to receive medication treatment for opioid use disorder regardless of a diagnosis of a comorbid mental or substance use disorder, a finding that conflicts with results from research indicating that females are less likely to receive substance use disorder treatment of all types (38). Females who had an additional diagnosis of a comorbid mental disorder only were the sole subgroup to be less likely to receive medication treatment for opioid use disorder. Given that females are more likely to visit primary care (39, 40), it is possible that, without primary care–based opioid use disorder treatment, this subgroup may have experienced service disparities. In contrast, females with an additional substance use disorder may seek specialty care that subsequently identifies and manages their opioid use disorder with medications. As noted, our study could not assess where diagnoses were made within the health system or via contact in the community or whether patients received mental health treatment. In general, however, levels of medication treatment for opioid use disorder were low, consistent with previous studies (44-47) and likely a result of numerous barriers to care (48, 49).

We note several limitations of this study. The use of EHRs and claims as the data source, rather than standardized assessments, had the potential for diagnosis misclassification. Misclassification can occur in either direction (e.g., a missed diagnosis because of

underdiagnosis or undercoding or overdiagnosis because of incorrect coding of, for example, physical dependence on prescribed opioids coded as opioid use disorder). Moreover, some patients may have been using buprenorphine for symptom management during an opioid taper rather than for opioid use disorder treatment. External medication orders were not captured in the EHRs (which was relevant to one study site with such orders), and medications dispensed from pharmacies not owned by the health plan were not captured if no insurance claim was submitted (e.g., self-pay, which was relevant to five sites with dispensings). In general, however, capture of health care utilization was almost complete at the five sites that received claims for outside services, and the community health system site reported providing comprehensive care to most of its patients.

Our treatment estimates were focused on opioid use disorder treatments that can be provided in primary care; therefore, data from methadone maintenance treatment were absent in our analysis, likely underestimating the true prevalence of treatment for opioid use disorder in our sample. We did not have data on the number of patients offered medications to manage opioid use disorder. Prevalence of posttraumatic stress disorder among our population was very low (0.3%; data not shown), which may reflect some underdiagnosis of this disorder. Identification of trauma exposure is important for accurate analysis (50), given both sex differences in trauma diagnoses (51) and impact of trauma on treatment outcomes (52). Our data were solely descriptive and did not offer explanations for the observed differences in prevalence of disease and treatment, and we cannot make conclusions about whether any comorbid conditions preceded or followed opioid use disorder. Our sample was predominantly White and therefore may not be generalizable to patients of other races or ethnicities who may be more or less likely to receive care in other settings (53, 54). Finally, the generalizability of our findings may have been limited by the fact that the sample included only patients regularly interacting with the health care systems whose data were used in this study.

CONCLUSIONS

This study provides robust, generalizable information about the 3-year prevalence of comorbid mental disorders and nonnicotine substance use disorders among male and female primary care patients with opioid use disorder, including those who received medication treatment for this disorder, in six large health care systems. The sample was large, had high geographic diversity, and represented both rural and urban communities. Health care systems should collect data on gender separately from data on sex assigned at birth, which would allow future studies to examine comorbid conditions and potential vulnerabilities among individuals of different gender identities, given reports of disproportionate substance use among gender minority groups. Future research should also address the reduced likelihood of medication treatment for opioid use disorder among females without other substance use disorders but with comorbid mental health conditions. Overall, the prevalence of comorbid conditions in the population studied suggests that primary care–based opioid use disorder treatment may need significant resources to adequately care for such patients. Continued integration of mental health services and substance use disorder services into primary care may decrease stigma and increase providers' ability to address the complex needs of patients with opioid use disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Approximately nine in 10 females and eight in 10 males with an opioid use disorder also had a comorbid mental health condition or other nonnicotine substance use disorder.
- Among patients with an opioid use disorder (with or without medication treatment), comorbid mental conditions were more common among females, whereas other nonnicotine substance use disorders were more prevalent among males.
- Females with a single comorbid mental health condition (i.e., no other nonopioid or nonnicotine substance use disorders) were less likely to receive medication treatment for opioid use disorder compared with males.

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TABLE 1.

Characteristics of primary care patients with opioid use disorder in six U.S. health care systems, fiscal years 2014–2016

	Females (N=7,431)		Males (N=6,548)		Total (N=13,979)	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**
Age in years						
16–17	109	1.5	84	1.3	193	1.4
18–25	963	13.0	1,164	17.8	2,127	15.2
26–35	1,413	19.0	1,444	22.1	2,857	20.4
36–45	1,300	17.5	1,029	15.7	2,329	16.7
46–55	1,522	20.5	1,190	18.2	2,712	19.4
56–65	1,216	16.4	1,119	17.1	2,335	16.7
66–75	543	7.3	383	5.8	926	6.6
>75	365	4.9	135	2.1	500	3.6
Race-ethnicity						
Hispanic	433	5.8	429	6.6	862	6.2
Non-Hispanic						
White	5,904	79.5	5,077	77.5	10,981	78.6
Black	490	6.6	434	6.6	924	6.6
Asian	72	1.0	104	1.6	176	1.3
Native American or Alaska Native	90	1.2	60	0.9	150	1.1
Hawaiian or Pacific Islander	15	.2	26	.4	41	.3
Multiracial	272	3.7	196	3.0	468	3.3
Other	49	.7	49	.7	98	.7
Unknown	106	1.4	173	2.6	279	2.0
Insurance type[a]	1,412	25.4	957	19.3	2,369	22.5
Medicare	1,412	25.4	957	19.3	2,369	22.5
Commercial	2,959	53.2	3,203	64.6	6,162	58.6
Medicaid	1,047	18.8	635	12.8	1,682	16.0
Uninsured	142	2.6	160	3.2	302	2.9
Charlson Comorbidity Index score ≥2[b]	430	5.8	461	7.0	891	6.4
Hepatitis C virus	543	7.3	692	10.6	1,235	8.8

	Females (N=7,431)		Males (N=6,548)		Total (N=13,979)	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**
HIV or AIDS	24	.3	108	1.6	132	.9
Active opioid use disorder[c]	6,902	92.9	6,052	92.4	12,954	92.7
Opioid use disorder in remission[c]	1,823	24.5	1,829	27.9	3,652	26.1
Opioid use disorder treatment[d]	1,312	17.7	1,561	23.8	2,873	20.6
Buprenorphine	1,283	17.3	1,522	23.2	2,805	20.1
Injectable extended-release naltrexone	61	.8	73	1.1	134	1.0
Nicotine use disorder	4,377	58.9	4,061	62.0	8,438	60.4

[a] Excludes HealthPartners because insurance status was unavailable (N=1,871 females and 1,593 males).

[b] The score is a sum of 17 comorbid conditions weighted according to the relative risk for 1-year mortality; a higher score indicates increased disease burden and risk of death.

[c] Not mutually exclusive categories because a patient may have received diagnoses of both active opioid use disorder and opioid use disorder in remission during the study period.

[d] Defined as one or more prescription or procedure codes for buprenorphine formulations used to manage opioid use disorder (transmucosal, implants, or sustained injection) or injectable extended-release naltrexone throughout the health system.

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TABLE 2.

Mental and other nonnicotine substance use disorder diagnoses among primary care patients with an opioid use disorder diagnosis during fiscal years 2014–2016 (N=13,979)[a]

	Females (N=7,431)		Males (N=6,548)	
Diagnosis	**%[b]**	**95% CI**	**%[b]**	**95% CI**
Any psychiatric	86.4	85.7–87.2	74.3	73.2–75.4
Depression	70.8	69.8–71.8	57.2	56.1–58.4
Anxiety	70.7	69.7–71.7	55.9	54.8–57.1
Serious mental illness[c]	19.9	18.9–20.8	16.0	15.1–16.9
ADHD	10.4	9.7–11.1	11.5	10.8–12.3
Eating disorder	3.8	3.3–4.2	.5	.4–.7
Any other nonnicotine substance use disorder	51.9	50.8–53.0	60.9	59.7–62.0
Alcohol	24.7	23.7–25.7	33.5	32.4–34.6
Cannabis	13.9	13.1–14.7	20.9	20.0–21.8
Stimulants	17.1	16.3–18.0	20.0	19.1–20.9
Other drugs	34.8	33.7–35.8	37.4	36.3–38.6
Any mental or other substance use disorder	90.8	90.1–91.5	85.9	85.0–86.7
Both mental and other substance use disorder	47.5	46.4–48.6	49.2	48.1–50.4
Other substance use disorder only	4.3	3.8–4.8	11.5	10.7–12.2
Psychiatric only	38.8	37.7–39.9	24.9	23.9–25.9
No mental or other substance use disorder	9.2	8.6–9.9	14.1	13.3–15.0

[a]ADHD, attention-deficit hyperactivity disorder.

[b]Prevalence estimates (and 95% confidence intervals)—adjusted for health system, age, and race-ethnicity—were obtained by fitting a logistic regression model and then applying marginal standardization.

[c]Any serious mental illness defined as bipolar disorder, schizophrenia, or other psychosis.

TABLE 3.

Prevalence of mental and other substance use disorder diagnoses among primary care patients with medication treatment of opioid use disorder[a] during fiscal years 2014–2016 (N=2,873)

	Females (N=1,312)		Males (N=1,561)	
Diagnosis	**%**[b]	**95% CI**	**%**[b]	**95% CI**
Any psychiatric	83	80–85	71	69–73
Any other substance use disorder	63	60–65	68	65–70
Any mental or other substance use disorder	90	88–91	86	84–88
Both mental and other substance use disorder	55	53–58	52	50–55
Other substance use disorder only	8	6–9	16	14–17
Psychiatric only	27	25–30	19	17–21
No mental or other substance use disorder	10	9–12	14	12–16

[a]Defined as one or more prescriptions or procedure codes for buprenorphine formulations used to manage opioid use disorder (transmucosal, implants, or sustained injection) or injectable extended-release naltrexone throughout the health system.

[b]Prevalence estimates (and 95% confidence intervals)—adjusted for health system, age, and race-ethnicity—were obtained by fitting a logistic regression model and then applying marginal standardization.